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Androgenic effects of autotransplants of adrenals in the accessory reproductive glands of adult castrated rats[1]

by

Dorothy PRICE and **Dwight J. INGLE**
(Department of Zoology and Ben May Laboratory for Cancer Research,
University of Chicago, Illinois)

In honor of Professor K. Ponse
on her sixtieth birthday

Evidence from many fields of research points to similarities between certain hormones of the adrenal cortex and the gonads, and to the existence of subtle functional interrelationships between these organs. Adreno-cortical hormones have been shown to have sex hormone-like action on the male and the female reproductive system under a variety of conditions. The effects may be androgenic, estrogenic or progestational. The subject has been ably reviewed by Parkes (1945), Ponse (1950), Courrier, Baclesse and Marois (1953), Moore (1953), Delost (1956) and many others.

In rats, early studies showed that castration of males at birth did not prevent the development of the ventral prostate gland (Price, 1936). Later, several workers demonstrated that the adrenals of rats and mice exert stimulating effects on accessory glands—prostate or seminal vesicles— in gonadectomized males (see Price, 1947 for a review). Recently, Delost (1953; 1954; 1956) reported stimulation of the ventral prostate, vas deferens

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and epididymis of the adult castrated field vole by adreno-cortical hormones. In contrast, in the castrated rat the stimulating action of the adrenals has been observed in one gland—the ventral prostate—in young animals under 35 days of age.

A direct approach has been made to the study of the androgenic activity of the adrenal cortex of the rat by transplantation of the adrenal glands directly into the seminal vesicles of castrated or castrated-adrenalectomized hosts (JOST, 1948; KATSH, GORDON and CHARIPPER, 1948; MOORE, 1953; JOST and GELOSO, 1954). This method was designed to detect low levels of androgenic hormone by placing the adrenal in contact with an end organ which might be sensitive to such stimulation. The results that were reported are conflicting. KATSH and his collaborators stated that adrenal cortical grafts in the seminal vesicles of adult rats established an " androgenic field " and prevented to a considerable degree the regressive changes in weight and histological structure in seminal vesicles and prostate glands following castration. The other workers obtained completely negative results or only slight effects.

To clarify the problem we have tested the androgenic activity of adrenals of adult rats by autotransplantation of these glands into the ventral prostates and seminal vesicles of castrated males. The criteria for determining androgenic stimulation were the histological structure and the weights of the accessory reproductive glands after experimental periods of one month or 3 months.

MATERIALS AND METHODS

Adult Sprague-Dawley rats that were 3½ to 4 months of age were divided into two groups. The first group of 9 rats was castrated and at the same time the adrenals of 6 were removed and transplanted as whole glands or as the entire capsule (with glomerulosa and possibly a little fasciculata) between the seminal vesicles and coagulating glands or onto the ventral prostatic lobes. In the second group of 12 rats, all were castrated as before, and in 8 the adrenals were removed and transplanted to the seminal vesicles (one or both whole adrenals were sutured to one seminal vesicle or one adrenal was put in each seminal vesicle) or onto the ventral prostate.

On the day of operation and on the succeeding day all operated rats received 5000 units of penicillin and 5 mg of streptomycin. The adrenalectomized rats with autotransplants were given 1 ml of adrenal cortical extract (Upjohn) on the day of operation and were maintained on 1% saline for one week. The rats were kept in an air-conditioned room at a temperature of 23°-25° C.

The first group was autopsied one month, and the second group, 3 months after operation. In addition, 4 normal males were sacrificed as controls. At autopsy, body weights and organ weights were obtained for all seminal vesicles and ventral prostatic lobes with the adrenals left in the organs in which they had been placed; adrenals were weighed in almost all of the control rats. In 3 cases, marked adhesions developed and bound together the left and right seminal vesicles (≠ 16) or the seminal vesicles and prostatic lobes (≠ 20 and ≠ 25). Since the adrenals which had originally been grafted into only one organ had been in close contact with both organs, no separation was made and the organs were weighed together. All of the weighed organs were fixed in Bouin's fluid and sectioned serially for histological study. The data on weights of seminal vesicles + coagulating glands (weighed together) and ventral prostates, and the evidence for stimulation in histological structure in seminal vesicles and ventral prostatic lobes are given in the table. A total of 25 adrenals were autotransplanted into 14 castrated males.

RESULTS

Most of the adrenal grafts were well incorporated in the accessory glands. Many of the grafts, especially in the 3-month experimental group contained normal-appearing cortical tissue in which all zones of the cortex were well developed. The medulla, when left in, degenerated and became necrotic. The grafts were functionally active and maintained the rats in good physical condition.

Weights of the accessory glands.

In order to draw conclusions as to the effects of adrenal grafts on the weights of the accessory organs to which they were transplanted, the probable weights of the adrenal grafts were estimated. A transplanted adrenal in the absence of the second one regenerates a mass of cortical tissue in 5 or 6 weeks that is equal to that of the original graft; if an enucleated adrenal (capsule plus glomerulosa) is transplanted, a single regenerating gland is larger than its original mass (INGLE, 1951). A further important factor is that the adrenals of castrated males hypertrophy, so that in the present experiments some regenerating grafts might have exceeded their original weight. The mean weight of one adrenal in the normal control males was 26 mg. An arbitrary value of 30 mg was selected as an estimated maximum weight for a regenerated graft, since this was the mean weight of a single adrenal gland in the controls that were castrated for one month.

There was a marked reduction in the weights of the accessory glands in controls following one month of castration and a further slight reduction after 3 months. If the estimated graft weights are subtracted from the weights of adrenal-implanted seminal vesicles + coagulating glands, the resulting weights are roughly equivalent to those in the appropriate castrated controls with two exceptions (≠ 13 and ≠ 17). One graft was implanted in each case except in ≠ 17 and ≠ 18 which had two. A large part of the weight in ≠ 13 (271 mg) was probably due to an abnormally large adrenal graft with masses of leucocytes. In ≠ 17, the right seminal vesicle was slightly heavier than might be expected, which may represent some degree of stimulation, especially in view of the histological findings. It must be concluded, therefore, that adrenal grafts did not prevent regression in the combined weight of the seminal vesicles + coagulating glands into which they were implanted, nor did the grafts seem to affect the weights of the opposite seminal vesicle + coagulating gland (≠ 15, ≠ 17, ≠ 18). The weights of 66 mg and 63 mg in ≠ 17 and ≠ 18 are not considered significantly above the castrated controls. Weights of the ventral prostates were not influenced by grafts in the seminal vesicles.

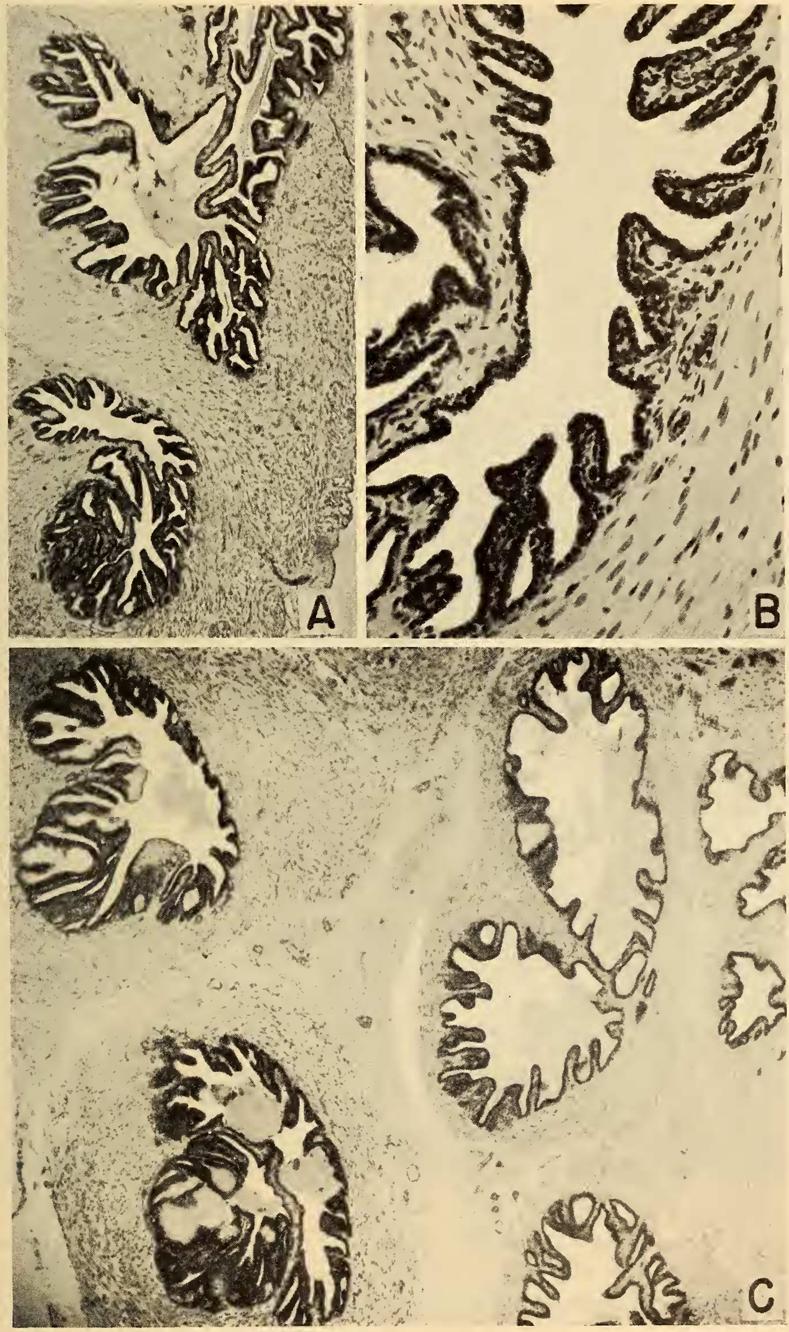
FIG. 1.

A) Left seminal vesicle of rat ≠ 17, castrated for 3 months and with two adrenal grafts in the right seminal vesicle. The gland is in a typically regressed state. × 50.

B) Portion of A) to show the involution of the epithelium. × 250.

C) Right seminal vesicle of rat ≠ 17 near an adrenal graft. Note the enlarged acini and secretion. × 50.

Fig. 1



In the ventral prostate, one whole adrenal or one enucleated gland was grafted into each of the two lobes in ≠ 20, ≠ 21 and ≠ 22, and one whole adrenal was placed between the lobes in ≠ 23; 2 whole adrenals were transplanted together into the prostate in ≠ 19, ≠ 24 and ≠ 25. Four weights indicate possible stimulation (right lobes of ≠ 20 and ≠ 21 and the prostates of ≠ 24 and ≠ 25). In 3 of these cases, accumulation of leucocytes or infiltration of muscle from adhesions with the body wall was found and might account for the heavier weight. Rat ≠ 24 was the only clear-cut case of a possible effect from the graft, and histological findings described below support this.

Histological structure.

Castration for one month or 3 months resulted in typical regression in histological structure in the seminal vesicles, coagulating glands and ventral prostates. These changes included reduction in epithelial height, pycnosis of the nuclei, loss of secretion granules in the seminal vesicles, loss of epithelial light areas in the ventral prostate, reduction in acinar size, loss of secretion and an increase in interacinous connective tissue. The regressive changes in the castrate were striking after one month, and some were even more marked after 3 months when almost all of the residual secretion had disappeared. The appearance of the seminal vesicle after 3 months of castration is shown in figure 1A and B; the ventral prostate involution is illustrated in figure 3A and C.

Seminal vesicles. — Adrenal grafts into seminal vesicles for one month had little or no effect upon the histological structure of the accessory gland except in the left seminal vesicle of ≠ 20, in which the amount of secretion in the ends of the acini appeared greater than in the castrated controls. However, there were no detectable effects on epithelial height. The stimulation in ≠ 20 was limited to acini that were close to the adrenal graft, while most of the gland was in the typical regressed state. When the grafts were left for 3 months they produced definite stimulation of the seminal vesicles in all 7 adrenal-implanted glands. The degree of stimulation ranged from slightly more secretion in the ends of the acini (≠ 15, ≠ 16), to more general increase in secretion and in acinar size (≠ 14, ≠ 18). In one case (right gland

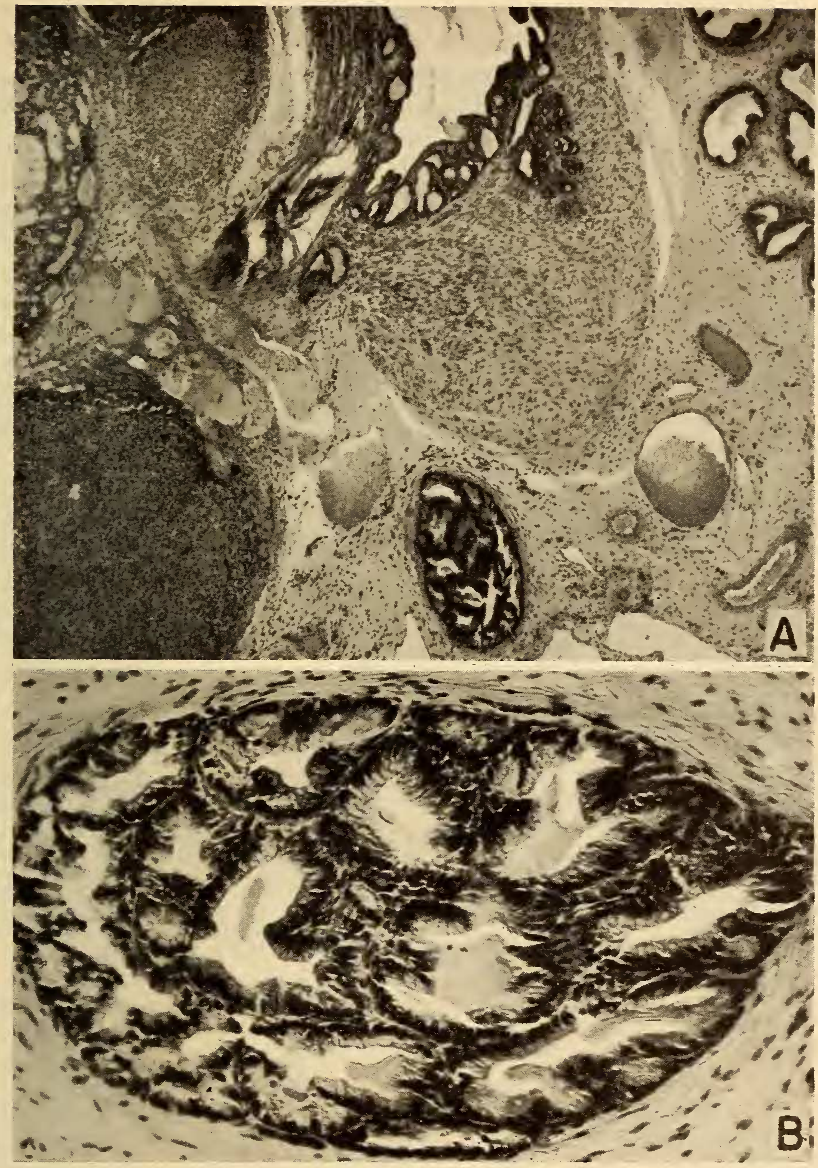


Fig. 2.

A) Right seminal vesicle of rat ≠ 17 at the level of the adrenal graft (lower left). Note the acinus near the graft. × 50.

B) Portion of A) to show the tall columnar epithelium of the acinus. Secretion granules were present in the cells. × 250.

of ≠ 17) there was more abundant secretion, larger acini and a few acini with tall columnar epithelium which had secretion granules (fig. 1C, 2A and B). The androgenic effect in all cases, however, was limited to localized regions fairly close to the adrenal grafts, and in these regions not all acini were stimulated. In ≠ 15, ≠ 17 and ≠ 18 the grafts had no effect on the structure of the opposite seminal vesicle (fig. 1A and B) which was indistinguishable from that of a castrated control.

Coagulating glands. — The results can be summarized by stating that there was a localized effect from adrenal grafts close to the acini in most cases in which the seminal vesicle was also stimulated. The effects included an increase in secretion, acinar size and epithelial height. Marked effects were found only after the longer period and were always localized.

Ventral prostate. — When adrenals were transplanted to the ventral prostate for one month, some degree of stimulation was found in 4 out of 7. This stimulation was evident in a slight to moderate increase in epithelial height and enlarged acinar diameter (≠ 20, ≠ 21, ≠ 22). In all cases only a few acini close to adrenal cortical tissue were affected. After 3 months there was marked stimulation in one of the 3 adrenal-implanted ventral prostates (≠ 24). There were many distended prostatic acini with moderate to tall columnar epithelium which had, in some places, epithelial light areas (fig. 3B, D). The stimulation was rather generalized but parts of the prostate at a greater distance from the grafts resembled the gland of a castrated control (fig. 3A, C). The 2 adrenal grafts were deeply incorporated in ≠ 24 but in the other two cases (≠ 23 and ≠ 25) the grafts did not become closely associated with the prostatic acini and no stimulation occurred. There were no effects from adrenal grafts in the prostates on the structure of the seminal vesicles.

FIG. 3.

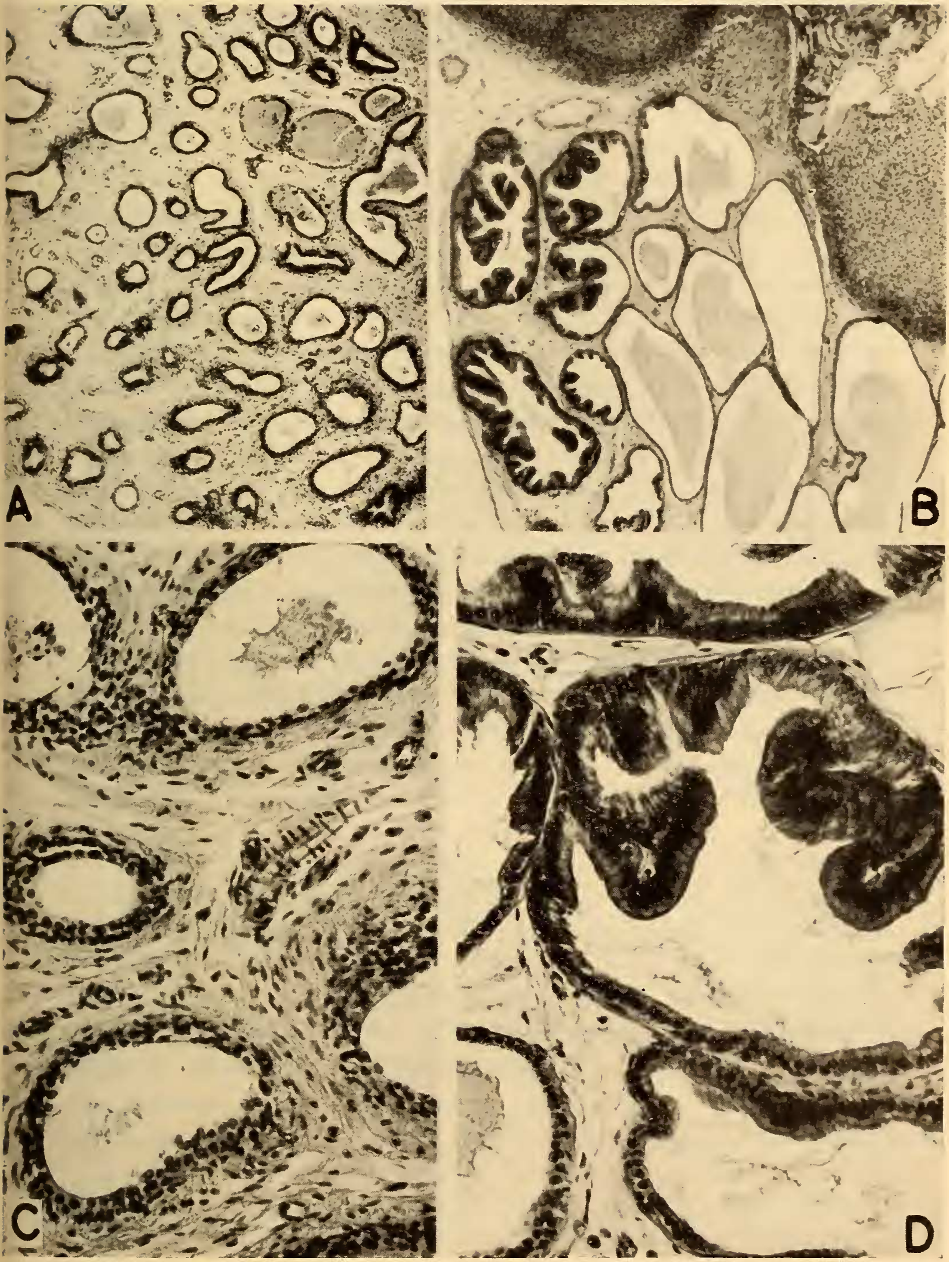
A) Ventral prostate gland of a rat castrated for 3 months. × 50.

B) Ventral prostate of rat ≠ 24; castrated and with 2 adrenal grafts in the ventral prostate. Note the adrenal graft (upper right) and the distended prostatic acini with tall epithelium. × 50.

C) Portion of A) to show the involuted epithelium. × 250.

D) Portion of B). Note the tall columnar epithelium with light areas in the cells. × 250.

Fig. 3



A comparison of the results on weights and on histological structure as reported in the table, emphasizes the fact that weight is not necessarily a dependable criterion for functional stimulation. In only two cases was a heavier gland associated with histological evidence of stimulation.

Discussion

The technique of testing the androgen-secreting activity of endocrine glands by placing them in close contact with sensitive end organs has been used for the study of secretion by adrenals, fetal testes and ovaries (Jost, 1948; Katsh, Gordon and Charipper, 1948; Katsh, 1950; Moore, 1953; Jost and Geloso, 1954; Ponse, 1954; Delost, 1956). It is a particularly useful method for detecting small amounts of hormone which are effective by local diffusion but might be ineffective via circulatory pathways.

Katsh and his collaborators and Jost and Geloso studied androgen secretion in the adult rat adrenal in critical experiments i.e. adrenal grafts in the seminal vesicles of castrated-adrenalectomized hosts for 30 days. The former investigators reported that an adrenal cortical graft in one seminal vesicle exerted an androgenic action which was also evident in the opposite seminal vesicle and the ventral prostate. An " androgenic field " with diminishing effects was established. It is not clear whether this implied a gradient of diffusion to the other accessory glands or some preferential distribution of adrenal androgen in the blood stream.

Jost and Geloso repeated these experiments in part. They did not study weights but on the basis of histology they concluded that any androgenic stimulation from the adrenal graft was barely discernable and very discrete.

The present study (1) confirmed some of the previous reports of androgenic action of adult adrenal cortical grafts in the seminal vesicles for 30 days, (2) demostrated the sensitivity of adult ventral prostates to adrenal androgens by placing grafts in the prostates and (3) clarified some aspects of the problem by extending the length of the experimental period to 3 months.

The results at 1 month are in agreement with the findings of Jost and Geloso in that the androgenic action of the grafts was slight and sharply localized in the organ which contained the graft. The observations of KATSH and his collaborators on maintenance of weights and the establishment of an androgenic field were not confirmed. There is no apparent explanation for this difference in results.

In our experiments, the androgenic effects of the grafts were clearer and more striking after 3 months. Again, however, the effects were limited to changes in histological structure in the gland that contained the graft. Only 2 cases suggested an effect on weights as well.

No attempt was made to correlate the amount of adrenal cortical tissue or its histological character with androgenicity. It appeared that a well-developed cortex with typical zonation was capable of exerting stimulating effects so that androgenicity is not a property of an undifferentiated cortex, a possibility suggested by KATSH.

Recently DELOST (1953; 1954; 1956) reported that in the field vole (*Microtus arvalis* P.) autotransplants of adrenal cortex stimulated the vas deferens locally; similar grafts in the ventral prostate and seminal vesicle were ineffective. He presented interesting evidence to support the concept that cortisone, not an adrenal androgen, is the stimulating hormone from the adrenal cortex in the vole. The adrenal androgen of the rat has not been identified (see COURRIER, BACLESSE and MAROIS, 1953).

SUMMARY

Autotransplants of adrenal glands in seminal vesicles or ventral prostates of castrated adult Sprague-Dawley rats exert a local stimulating effect on histological structure. The androgenic action is weak at 1 month but more marked at 3 months. The significance, if any, of the production of this androgen by the adult adrenal cortex of the castrate is not known.

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Table

Effects of autotransplants of adrenals into the accessory reproductive glands of adult castrated male rats [1]

Animal No.	Treatment	Body weight (g)	Weight (mg) of S.V. + C.G. L (no grafts)	R (no grafts)	L (with grafts)	R (with grafts)	Weight (mg) of V.P. (no grafts)	L (with grafts)	R (with grafts)
					Controls				
1	Normal control	382	614	649			500		
2		360	633	635			547		
3		356	604	570			411		
4		353	554	547			445		
5	Castrated 1 month	440	69	65			51		
6		398	96	74			64		
7		384	81	83			53		
8	Castrated 3 months	428	48	46			36		
9		418	54	52			40		
10		430	56	55			39		
11		412	55	53			55		
					Experimental animals				
12	Adrenal grafts in S.V. for 1 month	405			104	85	46		
13		434			109	271	42		
14	Adrenal grafts in S.V. for 3 months	460			77**	81**	25		
15		440		49	103*		39		
16		416		with L S.V.*	150*		34		
17		463	66			133***	49		
18		426		63	109**		43		
19	Adrenal grafts in V.P. for 1 month	435	66	68				126	
20		474	with L V.P.*	with R V.P.				135**	269
21		408	75	71				56**	89
22		418	89	62				57**	62*
23	Adrenal grafts in V.P. for 3 months	461	41	45				50	
24		475	56	57				150***	
25		337	with V.P.	56				178	

[1] S.V. + C.G. = seminal vesicle + coagulating gland; V.P. = ventral prostate.

* S.V. slightly increased secretion; V.P. slight increase in epithelial height.

** S.V. more abundant secretion; V.P. moderate increase in epithelial height, increase in acinar diameter.

*** S.V. increased secretion, enlarged acini, tall columnar epithelium with secretion granules; V.P. tall columnar epithelium with light areas, increased acinar diameter.